Remarks

Claims 14-29, 35, 36, and 39-47 are pending upon entry of the foregoing amendments.

Amendments to the Claims

Claim 14 has been amended to clarify that the release formulation which comprises the chemical molecules is *wholly contained* in each reservoir defined within the microtube. Support for this amendment is found, for example in FIGS. 7, 10, 11, and 12 and in the specification at page 16, lines 10-25.

Rejections Under 35 U.S.C. § 103

Claims 14-20, 22-29, 35, 36, 39, and 42-47 are rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 7,025,323 to Krulevitch, et al. ("Krulevitch") in view of U.S. Patent No. 5,797,898 to Santini Jr., et al. ("Santini") and U.S. Patent Application Publication No. 2003/0135201 to Gonnelli ("Gonnelli"). Claim 21 is rejected as obvious over Krulevitch, Santini, and Gonnelli, in further view of U.S. Patent No. 5,911,737 to Lee et al. ("Lee"). Claims 40 and 41 are rejected as obvious over Krulevitch, Santini, and Gonnelli, in further view of U.S. Patent No. 4,111,202 to Theeuwes ("Theeuwes"). These rejections are respectfully traversed.

Applicants' Claims Are All Non-obvious Over Krulevitch and Gonnelli

Neither Krulevitch nor Gonnelli teaches or remotely suggests a device in which a release formulation is disposed and wholly contained within a reservoir that is defined inside a microtube.

The Office Action, at page 3, alleges that "Krulevitch teaches an array of discrete microtubes (97) *defining* a reservoir (86-90)..." (emphasis added). This is incorrect and misleading. Microneedles 97 clearly do not in any reasonable way "define" reservoirs 86-90.

Moreover, the reservoirs in Krulevitch are *remote from* the microneedles and thus plainly do not teach locating reservoirs within the microneedles. That is, Krulevitch does not teach a microtube having a reservoir defined therein as required by Applicants' claims.

The same is true for Gonnelli. Gonnelli implicitly teaches having a separate drug reservoir "in communication with the microneedles" and that in "a preferred embodiment, the reservoir is in direct contact with the microneedles and [has] holes through which drug *could exit the reservoir and flow into the interior of* hollow or porous microneedles" (¶¶ 0043-0046) (emphasis added). Accordingly, Gonnelli does not remotely suggest a microtube that has a molecule storage reservoir defined therein. That is, Gonnelli does not teach locating a reservoir for a release formulation *wholly within* the microtube.

In addition, neither Krulevitch nor Gonnelli teaches or remotely suggests a microtube that has a *rupturable covering* that *encloses a first end of each reservoir*, and a means for rupturing the rupturable covering to cause the release formulation to be displaced through an opening *at that first end*. First, Krulevitch clearly discloses nothing about providing microneedles with a rupturable covering. There would be no reason to do so, given Krulevitch's teaching of alternative means for controlling fluid flow through the microneedles.

Second, Gonnelli's disclosure of covering the microneedle opening with an ion-selective membrane plainly **teaches away** from Applicants' claimed devices, because membrane 130 is not intended to rupture. In fact, if it ruptures, then it fails to work as intended. i.e., it will no longer "selectively allow certain species (e.g., one or more desired analytes) to pass therethrough while substantially blocking certain other species (e.g., one or more undesired species" (¶ 0061).

In sum, nothing in Krulevitch or Gonnelli can possibly be construed as teaching one of ordinary skill in the art all of the elements defining Applicant's claimed devices and methods.

Applicants' Claims Are All Non-obvious Over Krulevitch and Santini

Neither Krulevitch nor Santini teaches or remotely suggests a device in which a release formulation is disposed and wholly contained within *a reservoir that is defined inside a microtube*. First, in both Krulevitch and Santini, the reservoir is located in a substrate, not in a microtube. Accordingly, neither reference remotely suggests having a release formulation disposed wholly within the microtube reservoir as required by Applicants' claimed devices.

Second, Krulevitch admittedly fails to disclose a rupturable covering enclosing a first end of reservoir in the microtube. Since Santini does not remotely teach anything about microneedles or microtubes, it plainly cannot teach placing a rupturable covering over the end of a microtube. The Examiner's analysis to the contrary is improper and insufficient to establish a *prima facie* case of obviousness. "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." KSR Int'l Co. v. Teleflex Inc., 550 U.S. ___ (2007) (Slip Op. at 14).

The Examiner alleges that it would have been obvious in view of Santini to place a metallic covering over the microneedles of Krulevitch in order to prevent leakage and contamination of the reservoir contents. A person of ordinary skill in the art trying to prevent leakage or contamination—the hypothetical problem or reason imagined by the Examiner—has a nearly infinite variety of technical options to choose from in try to meet such objectives. For instance, the contamination and/or leak prevention means may be located at the reservoir or at either or both ends of the microneedles, the means may utilize a mechanical or electromechanical

valve, the means may focus on the formulation itself (e.g., making it less fluid), or the means may involve rupturable or non-rupturable materials and operational designs, just to name of few of the myriad variables one skilled in the art might or might not utilize depending on a host of engineering and practical considerations. Accordingly, it would have required more than mere common sense for the artisan of ordinary skill to leap from the prior art teachings of Krulevitch, alone or in combination with Santini, to derive Applicants' claimed devices.

In fact, it is apparent that the combination posited by the Examiner is only obtained using ex post reasoning, because Krulevitch teaches preventing leakage in a completely different way. "A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning." KSR Int'l Co. v. Teleflex Inc., 550 U.S. ___ (2007) (Slip Op. at 17). Specifically, Krulevitch teaches that "channel sealing is *dependent* on selective poly (dimethylsiloxane) (PDMS) surface modifications," and that "[t]he polymer channel should be hydrophobic and pneumatic fluid should be hydrophilic when using hydrophilic reagents or vice versa... for [a] leak proof seal." (Col. 6, Lns. 56-60) (emphasis added). Because Krulevitch teaches controlling leaks in the device by the use of a specific type of *polymer* located *in the substrate/channel structures*, it **teaches away** from controlling leaks with a *metallic* cover at the *end of the microneedle*.

Claim 21 Is Not Obvious Over the Combination

of Santini or Gonnelli in View of Lee.

Contrary to the Examiner's apparent misunderstanding of Lee, the reference plainly does not teach a *microtube* that is made of a shape memory *alloy*. Rather, Lee discloses microfabricated therapeutic actuators comprising shape memory **polymer** microtubing that may

be used for retaining and the releasing an embolic platinum coil. (Abstract and claim 1). While Lee, at Col. 1, Lns. 30-36, teaches that prior art microgrippers may be actuated by shape-memory alloy films or wires deposited on or connected to the jaws of the microgrippers, this is merely a characterization of a prior art microgripper and is not a description of an alloy microtube. Furthermore, nothing in Lee remotely suggests a device having an array of discrete microtubes.

Lee also fails to supplement the other deficiencies of either Santini or Gonnelli to meet all elements defining Applicants' claimed devices and methods. Accordingly, the combination of Lee and Santini and Gonnelli fails to establish a *prima facie* case of obviousness.

Claims 40 and 41 Are Not Obvious Over the Combination of Krulevitch and Gonnelli in View of Theeuwes.

Nothing in Theeuwes remotely suggests a device having an array of discrete microtubes, a device constructed with a metal or an alloy, or a device with a rupturable covering. One of ordinary skill in the art would have had no reason to combine Theeuwes with Krulevitch and Gonnelli. The Examiner contends that it would have been obvious to combine the "osmotic delivery system of Theeuwes with the microneedle array of Krulevitch and Gonnelli in order to facilitate expansion of the expandable member without electronics." This ex post reasoning not only is unsupported conjecture, it also is irrelevant to the claims and primary references.

First, neither Krulevitch nor Gonnelli are taught to operate by permitting selected molecules from outside the reservoir to diffuse to the expanding material to cause the expanding material to expand and displace the release formulation in an amount effective to rupture the rupturable covering and discharge the release formulation from the reservoir. The Examiner has identified no evidence to suggest a specific market or design need to modify the teachings of

Krulevitch and Gonnelli to omit electronics from the device. Moreover, Applicants' claimed devices do not necessarily operate without electronics. Indeed, the Examiner has failed to articulate with any specificity why or how one of ordinary skill in the art would have been led to modify Krulevitch's *programmable, multi-dosage* delivery device (which uses a powered heater to create a vapor bubble to release reagent from a plurality of channels) to somehow substitute an osmotic delivery system, which provides *continuous* release. It is not predictable one could achieve with the Theeuwes osmotic system the same control of release kinetics obtainable with the powered heater means of Krulevitch's device. Therefore, a person of ordinary skill in the art simply would not have combined Theeuwes with Krulevitch for the reason alleged by the Examiner.

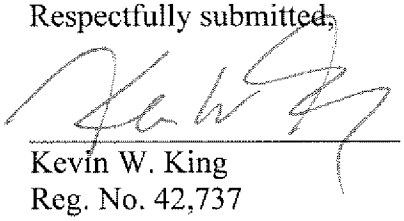
Moreover, Theeuwes fails to supplement the other deficiencies of either Krulevitch or Gonnelli to meet all elements defining Applicants' claimed devices and methods. Accordingly, the combination of Theeuwes and Krulevitch and Gonnelli fails to establish a *prima facie* case of obviousness.

Conclusions

For the foregoing reasons, it is submitted that all of Applicants' claims are non-obvious over the cited prior art. Prompt allowance of each of pending claims 14-29, 35, 36, and 39-47 is therefore respectfully solicited.

The undersigned kindly invites the Examiner to contact him by telephone (404.853.8068) if any outstanding issues can be resolved by conference or examiner's amendment.

Respectfully submitted,



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